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Relationship between vascular endothelial growth factor and left ventricular dimension in patients with acute myocardial infarction



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ABSTRACT

Background: Although vascular endothelial growth factor (VEGF) is elevated in patients with acute myocardial infarction (AMI), the clinical significance of its elevation remains unclear. The present study was designed to determine the relationship between VEGF and left ventricular dimension in patients with AMI.

Methods and results: Plasma VEGF levels were examined by enzyme-linked immunosorbent assay daily for one week and then weekly for four weeks in 38 patients with AMI (65.4 ± 1.7 years). Left ventriculography was performed at 14 days, 6 months, and 2 years after the onset of AMI. Plasma VEGF levels were significantly elevated and reached a peak on day 6. Peak plasma VEGF levels positively correlated with both end-diastolic and end-systolic volume indices at 14 days after the onset of AMI. When patients with AMI were divided into two groups according to plasma VEGF levels on admission, left ventricular volume indices were higher in the high VEGF group than in the low VEGF group at the subacute phase of AMI (14 days). These differences were no longer present in the chronic phase of AMI.

Conclusion: Plasma VEGF levels were increased in patients with AMI, and peak levels were associated with left ventricular volume indices in the subacute phase, suggesting an important role of endogenous VEGF in the left ventricular dimension in patients with AMI.

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Introduction

Vascular endothelial growth factor (VEGF) [1] is an important endothelial cell-specific mitogen. VEGF enhances vascular permeability [2,3], accelerates collateral formation in ischemic myocardium [4–6], and promotes tissue repair after wound healing [7]. Several reports have demonstrated that patients with acute myocardial infarction (AMI) have elevated circulating VEGF levels as compared with healthy subjects [8–12]. Treatment with exogenous VEGF promoted vessel formation in ischemic myocardium

and improved ventricular function in patients with ischemic heart diseases [13,14]. On the other hand, granulocyte colony stimulating factor upregulated VEGF and improved survival by accelerating neovascularization in a rabbit model of myocardial ischemia [15]. However, the clinical significance of endogenous VEGF in patients with AMI has not been fully understood.

The relationship between plasma VEGF levels and subsequent cardiac dimension in patients with AMI is controversial. Soeki et al. defined the remodeling group as having an increase in left ventricular end-diastolic volume index (LVEDVI) more than 5 ml/m^2 at 3 months after the onset of AMI. They found no changes in VEGF levels between the remodeling group and the non-remodeling group [11]. On the other hand, Suzuki et al. defined the remodeling group as showing an increase in LVEDVI at one month after the onset of AMI and demonstrated that peak VEGF levels were significantly higher in the remodeling group than in the non-remodeling group

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[12]. However, there are no reports investigating the relationship between peak VEGF levels and left ventricular volume indices at the more chronic phase of AMI, such as 6 months or 2 years after the onset of AMI. Therefore, the aim of the present study was to examine the time course of plasma VEGF levels in patients with AMI, and to investigate the correlation between plasma VEGF levels and left ventricular dimension in the early and chronic phase of AMI.

Methods

Patient characteristics

The present study included 38 patients (27 males and 11 females, mean age 65.4 ± 1.7 years) with AMI who were admitted to the National Hospital Organization Kagoshima Medical Center within 12 hours after the onset of symptoms and had successful reperfusion therapy with percutaneous coronary intervention from August 2001 to July 2002. The clinical characteristics and medication in all patients with AMI are shown in Tables 1 and 2, respectively. The diagnosis of AMI was based on the findings of severe prolonged chest pain for at least 30 min, ST-segment elevation of at least two continuous leads by a standard 12-lead electrocardiogram, and elevation of serum creatine kinase (CK)-MB isozyme to more than twice the upper limit of normal range. Patients with AMI more than 12 h from the onset and those with AMI who had already received heparin treatment before admission to our hospital were excluded in the present study. Patients with preexisting heart diseases including previous myocardial infarction, valvular heart disease, and cardiomyopathy were also excluded. Other exclusion criteria were renal dysfunction requiring dialysis and evidence of malignant and inflammatory diseases. All patients were monitored in our intensive care unit and entered into the cardiac rehabilitation programs in our hospital. Age-matched 22 subjects (13 men and 9 women, mean age 63.7 ± 1.5 years) having atypical chest pain with angiographically normal coronary arteries and a normal left ventriculogram served as control subjects. The investigation conforms to the principles outlined in the

Declaration of Helsinki, and it was approved by the Institutional Review Board in our hospital. Written informed consent was obtained from each patient with AMI and also from the control subjects.

Blood sampling

Peripheral blood samples were obtained immediately before administration of heparin at the time of admission, daily for one week, and then weekly for four weeks in patients with AMI. B-type natriuretic peptide (BNP) was also examined.

Measurement of VEGF levels

Plasma samples for the measurement of VEGF were placed in ethylenediaminetetraacetic acid-coated tubes containing 500 IU/ml of aprotinin, centrifuged immediately at 3000 rpm for 10 min at 4°C , and stored at -80°C until analysis. Plasma VEGF levels were determined using a specific enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The minimal detection limit of this ELISA was 31.2 pg/ml. VEGF levels were defined as zero if the values were less than the minimal detection limit. VEGF assay was performed by an investigator blinded to the sources of the samples. Intra-assay and inter-assay variations were 5.6% and 9.8%, respectively.

Ultrasound cardiography

Standard two-dimensional and Doppler echocardiographic examinations were performed at admission, at 28 days, 6 months, and 2 years after the onset of AMI. Left ventricular end-diastolic diameter (LVDd) and left ventricular end-systolic diameter (LVDs) were measured by two-dimensional and M-mode echocardiography. Ejection fraction (EF, Simpson method) was calculated according to the standard formula.

Table 1
Patient characteristics in high VEGF group and low VEGF group.

	Total (n = 38)	High (n = 12)	Low (n = 26)	p-Value
Age (years)	65.4 ± 1.7	69.8 ± 3.5	63.3 ± 1.8	NS
Sex (%)				
Male	27 (71.0)	10 (83.3)	17 (65.4)	NS
Female	11 (29.0)	2 (16.7)	9 (34.6)	NS
BMI (kg/m^2)	24.4 ± 0.5	25.3 ± 1.0	24.0 ± 0.5	NS
Risk factors				
Hypertension (%)	24 (63.2)	5 (41.7)	9 (34.6)	NS
Hyperlipidemia (%)	17 (44.7)	4 (33.3)	13 (50)	NS
Diabetes mellitus (%)	16 (42.1)	4 (33.3)	12 (46.2)	NS
Smoking (%)	12 (31.6)	6 (50.0)	6 (23.1)	NS
Killip classification				
I	30 (78.9)	8 (66.7)	22 (84.6)	NS
II	8 (21.1)	4 (33.3)	4 (15.3)	NS
Time to reperfusion (h)	3.9 ± 0.4	3.3 ± 0.4	4.1 ± 0.6	NS
Diseased vessels				
Single-vessel disease	24 (63.2)	5 (41.7)	19 (73.1)	NS
Multivessel disease	14 (36.8)	7 (58.3)	7 (26.9)	NS
Rentrop collateral grade				
0/1	23 (60.5)	6 (50.0)	17 (65.4)	NS
2/3	15 (39.5)	6 (50.0)	9 (34.6)	NS
CI ($\text{L}/\text{min}/\text{m}^2$)	3.59 ± 0.2	3.2 ± 0.19	3.8 ± 0.2	NS
PCWP (mmHg)	13.7 ± 1.1	15.9 ± 2.8	12.8 ± 1.1	NS
LVEF (UG) (%)	58.2 ± 1.9	52.7 ± 3.7	60.9 ± 1.9	NS
Peak CK (IU/L)	3029 ± 320	3614 ± 661	2759 ± 352	NS
Peak BNP (pg/ml)	240 ± 31	260 ± 75	229 ± 37	NS

Values are expressed as number (percentage) of patients or mean value \pm SE. VEGF, vascular endothelial growth factor; NS, not significant; BMI, body mass index; CI, cardiac index; PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction; UCG, ultrasound cardiography; CK, creatine kinase; BNP, B-type natriuretic peptide.

Table 2

Medication on admission, at discharge, at 6 months and 2 years after the onset of AMI in high VEGF group and low VEGF group.

	On admission (%)			Discharge (%)			6 months (%)			2 years (%)		
	High (n = 12)	Low (n = 26)	p-Value	High (n = 12)	Low (n = 26)	p-Value	High (n = 6)	Low (n = 21)	p-Value	High (n = 4)	Low (n = 7)	p-Value
ACE inhibitor	1 (8.3)	1 (3.8)	NS	6 (50.0)	11 (42.3)	NS	2 (33.3)	7 (33.3)	NS	2 (50)	2 (28.6)	NS
Angiotensin receptor blocker	0 (0)	3 (11.5)	NS	5 (41.7)	13 (50.0)	NS	4 (66.6)	12 (57.1)	NS	2 (50)	4 (57.1)	NS
Calcium-channel blocker	4 (33.3)	7 (26.9)	NS	4 (33.3)	7 (26.9)	NS	1 (16.7)	6 (28.5)	NS	1 (25)	4 (57.1)	NS
Spironolactone	0 (0)	0 (0)	NS	2 (16.7)	5 (19.2)	NS	1 (16.7)	4 (19.0)	NS	1 (25)	0 (0)	NS
Statin	0 (0)	2 (7.7)	NS	3 (25.0)	9 (34.6)	NS	3 (50.0)	7 (33.3)	NS	2 (50)	3 (42.9)	NS

Values are expressed as number (percentage) of patients. AMI, acute myocardial infarction; VEGF, vascular endothelial growth factor; ACE, angiotensin converting enzyme; NS, not significant.

Cardiac catheterization

All patients with AMI were transferred to the catheterization laboratory, and underwent percutaneous coronary intervention (PCI) immediately after admission ($n=38$). Right-sided cardiac catheterization was performed for the measurement of pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) just before PCI. No patients had a culprit lesion at the left main trunk, and post-PCI restenosis was not observed in any patients with AMI. Time to reperfusion, diseased vessels, and Rentrop collateral grading are shown in Table 1. Left ventriculography was performed for the measurement of LVEDVI and left ventricular end-systolic volume index (LVESVI) using computer-assisted analysis system (QCA-CMS; Goodman Co., Ltd., Nagoya, Japan). For the follow-up study, cardiac catheterization was also performed at 14 days ($n=27$), 6 months ($n=27$), and 2 years ($n=11$) after the onset of AMI.

Statistical analysis

All data are shown as means \pm SE. Statistical analysis was performed using StatView J-5.0 (SAS Institute Inc., Cary, NC, USA). Categorical variables were compared by chi-square analysis with Fisher's exact probability. The plasma levels of VEGF over the time course of AMI were analyzed using analysis of variance (ANOVA) for repeated measures. Comparison of parameters between two groups was performed with the unpaired Student's *t*-test. The relationship between VEGF levels and left ventricular volume indices or other parameters was examined by linear regression analysis. Values of $p < 0.05$ were considered statistically significant.

Results

Plasma VEGF levels in patients with AMI

Fig. 1 shows the time course of plasma VEGF levels for 4 weeks in patients with AMI. Plasma VEGF levels from day 5 to day 7 were significantly higher in patients with AMI than those (27.9 ± 14.4 pg/ml) in control subjects. Plasma VEGF levels reached a peak on day 6 (104.5 ± 27.2 pg/ml), and gradually decreased thereafter. We then investigated the relationship between the peak plasma VEGF levels and the clinical parameters in patients with AMI. Peak plasma VEGF levels showed no correlations with echocardiographic or hemodynamic parameters on admission. In addition, peak plasma VEGF levels had no correlations with age, gender, risk factors, or peak CK levels in patients with AMI. In 38 patients with AMI, 27 patients received cardiac catheterization at 14 days after the onset of AMI, and LVEDVI as well as LVESVI were calculated by area-length methods as described above. As shown in Fig. 2, peak plasma VEGF levels positively correlated with LVEDVI ($r=0.51$, $p=0.0057$) and LVESVI ($r=0.57$, $p=0.0016$) in these 27 patients with AMI. We further performed follow-up

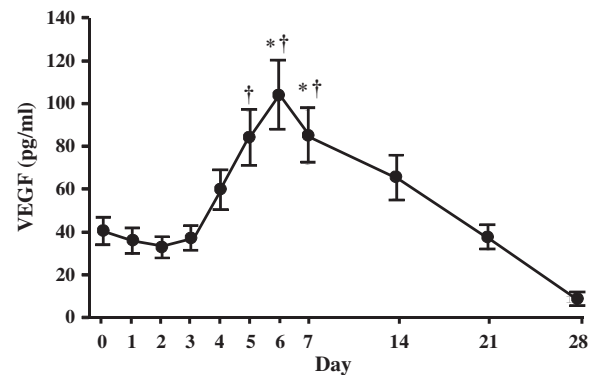


Fig. 1. Time course of plasma vascular endothelial growth factor (VEGF) levels in patients with acute myocardial infarction. Plasma VEGF levels reached a peak on day 6, and gradually decreased thereafter. Values are mean \pm SEM. * $p < 0.05$ compared with values on admission. † $p < 0.05$ compared with values in the control subjects.

cardiac catheterization at 6 months ($n=27$) and 2 years ($n=11$) after the onset of AMI, and examined LVEDVI and LVESVI in these patients. However, the correlations seen at 14 days and 6 months after the onset of AMI disappeared at 6 months and 2 years after the onset of AMI.

Therefore, we investigated the correlation between peak plasma VEGF levels and changes in LVEDVI and LVESVI from 14 days to 6 months and from 14 days to 2 years after the onset of AMI. As shown in Fig. 3, peak plasma VEGF levels had inverse correlations with changes in LVEDVI and LVESVI from 14 days to 6 months after the onset of AMI (Fig. 3A and B). Although the number of AMI patients was less, similar correlations were observed between the peak plasma VEGF levels and changes in LVEDVI and LVESVI from 14 days to 2 years (Fig. 3C and D).

High VEGF group and low VEGF group

In 38 patients with AMI, 26 patients had plasma VEGF levels less than the minimal detection limit of VEGF assay on admission. Therefore, we investigated whether clinical parameters including echocardiographic and hemodynamic parameters as well as plasma VEGF levels in these 26 AMI patients (low VEGF group) were different from those in the remaining 12 AMI patients (high VEGF group). Fig. 4 illustrates the time course of plasma VEGF levels in these two groups. In the high VEGF group, the plasma VEGF levels remained elevated until 21 days after the onset of AMI as compared with the low VEGF group. The differences in plasma VEGF levels between the two groups disappeared on day 28. The clinical characteristics and the medication in the high VEGF group and the low VEGF group are shown in Tables 1 and 2, respectively. There were no significant differences between the two groups. In 27 AMI patients in whom cardiac catheterization was performed at 14 days after the onset of AMI, 6 patients belonged to the high VEGF group and 21

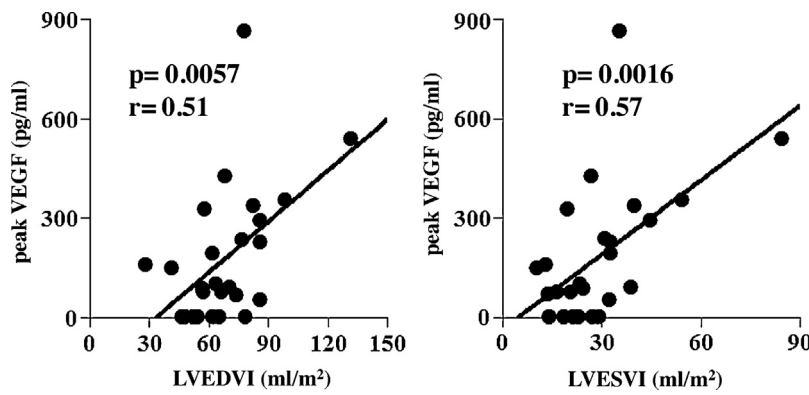


Fig. 2. Correlations between peak plasma VEGF levels and LVEDVI (left) and between peak plasma VEGF levels and LVESVI (right) at 14 days after the onset of acute myocardial infarction. Significant positive correlations were observed between peak plasma VEGF levels and LVEDVI ($r=0.51$, $p=0.0057$) and between peak plasma VEGF levels and LVESVI ($r=0.57$, $p=0.0016$). VEGF, vascular endothelial growth factor; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index.

patients belonged to the low VEGF group. In these 27 AMI patients, both LVEDVI and LVESVI were significantly higher in the high VEGF group than in the low VEGF group (Fig. 5). We also investigated the changes in LVEDVI and LVESVI from 14 days to 6 months after the onset of AMI. Both LVEDVI and LVESVI in the high VEGF group significantly decreased, and those in the low VEGF group significantly increased at 6 months after the onset of AMI. The differences in LVEDVI and LVESVI between the two groups observed at 14 days disappeared at 6 months after the onset of AMI. There were no significant differences in LVEDVI and LVESVI between the two groups at 2 years after the onset of AMI as well (data not shown).

Discussion

The present study demonstrated that plasma VEGF levels were significantly elevated from day 5 to day 7 in patients with AMI compared with the levels in the control subjects. These findings were supported by previous studies that patients with AMI have elevated circulating VEGF levels compared with control subjects [8–12]. Precise mechanisms of plasma VEGF elevation in patients with AMI are not fully understood. Hypoxia is a strong inducer of VEGF expression in the heart [16]. Inflammation is another important factor activating plasma VEGF levels in patients with

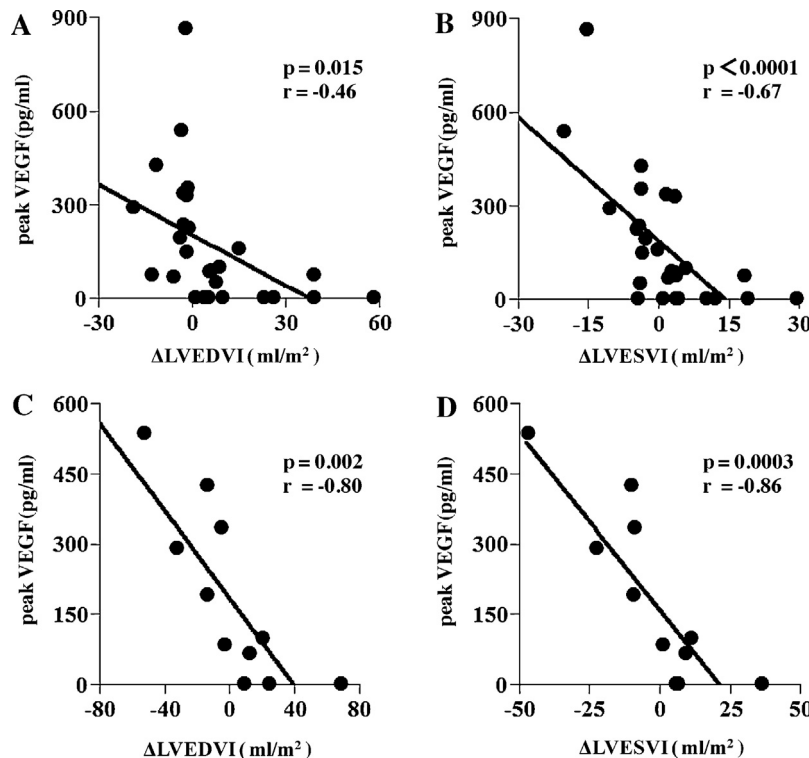


Fig. 3. Correlations between peak plasma VEGF levels and changes in LVEDVI and LVESVI from 14 days to 6 months and from 14 days to 2 years after the onset of acute myocardial infarction. Peak plasma VEGF levels had inverse correlations with changes in LVEDVI (A, from 14 days to 6 months, $r=-0.46$, $p=0.015$; C, from 14 days to 2 years, $r=-0.80$, $p=0.002$) and with LVESVI (B, from 14 days to 6 months, $r=-0.67$, $p<0.0001$; D, from 14 days to 2 years, $r=-0.86$, $p=0.0003$). Δ LVEDVI, changes in LVEDVI; Δ LVESVI, changes in LVESVI. VEGF, vascular endothelial growth factor; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index.

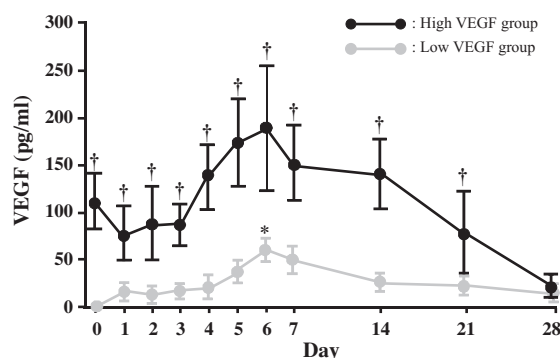


Fig. 4. Time course of plasma VEGF levels in the high VEGF group and the low VEGF group. Plasma VEGF levels in the high VEGF group (black circles, $n = 12$) were significantly higher than those in the low VEGF group (gray circles, $n = 26$) on admission, and remained elevated for 21 days after the onset of acute myocardial infarction. * $p < 0.05$ compared with values on admission. † $p < 0.05$ compared with the low VEGF group. VEGF, vascular endothelial growth factor.

AMI [17,18]. Specifically, Sasaki et al. previously demonstrated that peripheral blood mononuclear cell, an independent predictor of left ventricular remodeling after AMI [19], is considered the source for circulating VEGF in patients with AMI [20]. Alternatively, ventricular stretch or expansion may also augment VEGF expression in the heart, leading to an increase in plasma VEGF levels in patients with AMI. Li et al. reported that mechanical stretch in the left ventricle induced an increase in VEGF gene expression [21]. In the present study, the peak plasma VEGF levels positively correlated with left ventricular volume indices in the subacute phase of AMI. Therefore, VEGF may be released from the heart in relation to left ventricular stretch after AMI. As for the possible molecular mechanisms, the previous investigations demonstrated that stretch-induced VEGF upregulation is mediated at least in part by tumor growth factor

(TGF)- β [21,22], hypoxia inducible factor (HIF)1 α [23], and nuclear factor κ B (NF κ B) [24].

Previous investigators showed a significant positive correlation between peak VEGF levels and LVEDVI at four weeks after the onset of AMI [12]. However, there have been no reports demonstrating the relationship between peak VEGF levels and left ventricular volume indices at the chronic phase of AMI. In the present study, we demonstrated that peak plasma VEGF levels correlated not only with LVEDVI but also with LVESVI at the subacute phase of AMI (14 days after the onset of AMI). Moreover, peak plasma VEGF levels showed inverse correlations with changes in LVEDVI and LVESVI from 14 days to 6 months as well as from 14 days to 2 years after the onset of AMI. The differences in LVEDVI and LVESVI between the high and low VEGF groups observed at the subacute phase of AMI disappeared at the chronic phase of AMI. These findings indicated that the higher the peak plasma VEGF levels reached, the larger the left ventricular volume progressed at the subacute phase of AMI. In addition, the higher the peak plasma VEGF levels reached, the smaller the left ventricular volume size changed at the chronic phase of AMI. In experimental animal models of AMI, VEGF protein injection or VEGF gene transfer reduced scar size in the left ventricle [25,26]. Although the present study did not investigate the causal relationship between VEGF and ventricular remodeling [27], the elevation of endogenous VEGF after the onset of AMI is considered beneficial with regard to left ventricular remodeling via infarct size reduction.

Study limitations

There are several limitations to this study. This was a retrospective observational study and the number of patients was relatively small. As we have not performed left ventriculography on admission, we could not evaluate changes in left ventricular volume indices from acute to subacute or from acute to chronic phase

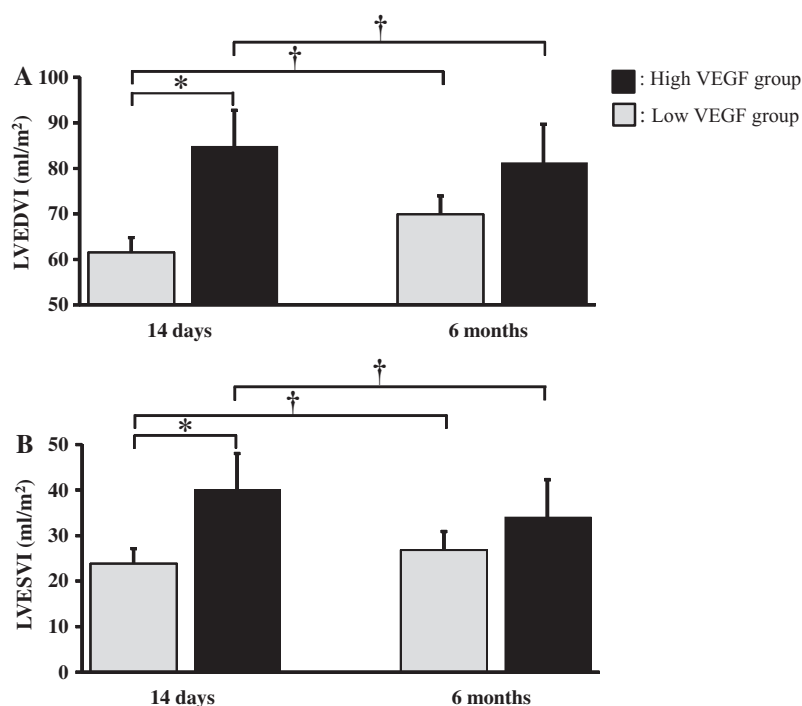


Fig. 5. LVEDVI and LVESVI in the high VEGF group and in the low VEGF group at 14 days and 6 months after the onset of AMI. LVEDVI (A) and LVESVI (B) were significantly higher in the high VEGF group (black bar) than in the low VEGF group (gray bar) at 14 days after the onset of AMI. LVEDVI and LVESVI in the high VEGF group significantly decreased, and those in the low VEGF group significantly increased at 6 months after the onset of AMI. * $p < 0.05$ compared with the low VEGF group. † $p < 0.05$ compared with 14 days after the onset of AMI in each group. LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; VEGF, vascular endothelial growth factor; AMI, acute myocardial infarction.

of AMI. On the other hand, we do not have results of long-term follow-up data >2 years. In addition, we did not investigate the presence of concomitant ischemic diseases such as cerebrovascular disease and peripheral arterial disease in these patients with AMI. A randomized controlled study based on a greater number of patients with a longer observational period is needed to confirm our results. Another limitation was the influence of heparin in measuring the plasma VEGF levels, because heparin is known to reduce plasma VEGF levels [8,28], and heparin is routinely used during the treatment of AMI for a few days. In the present study, patients with AMI who had already received heparin treatment before admission to our hospital were excluded, so that the plasma VEGF levels on admission were without the influence of heparin. We used 100 IU/kg intravenous bolus injection of heparin at the time of emergency cardiac catheterization, followed by continuous infusion at the dose of 0.1 IU/kg/min for three days. Therefore, the plasma samples from day 1 to day 3 were obtained under treatment with heparin, and there is a possibility that plasma VEGF levels within the first three days might be underestimated. We confirmed that ELISA itself for measuring VEGF was substantially unaffected by the administration of heparin.

Conclusions

In conclusion, the present study has demonstrated that plasma VEGF levels are increased in patients with AMI as compared with the control subjects, and that peak plasma VEGF levels correlated positively with left ventricular volume indices at the subacute phase of AMI. This study provides a new insight into the significance of VEGF in association with left ventricular dimension in patients with AMI.

Conflict of interest

There are no conflicts of interest.

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